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Inclusion criteria for outcomes of studies in Cochrane Systematic Reviews should be more clearly reported

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Abstract

Objective: to survey how outcomes in recent Cochrane Reviews were defined and used for inclusion of studies and how this compares with guidance on preventing outcome reporting bias.

Study Design and Setting: A survey of Cochrane reviews. We extracted data on the outcomes and how the outcomes were used for inclusion of studies in the review.

Results: We included 52 reviews with a mean of 8.4 (SD 4.3) outcomes. Of all reviews 47 (90%) used primary and secondary outcomes as the names for their review's outcomes, but without further definition. None reported using a core outcome set. Forty reviews (77%) did not explain if they used outcomes for inclusion of studies, 8 (15%) stated that studies were included if they reported either primary or secondary outcomes, 1 (2%) reported that outcomes were not used for inclusion and for 3 (6%) this was unclear.

Conclusions: In a sample of Cochrane Reviews, most reviews did not state if outcomes were used for inclusion of studies. Better explanation of inclusion decisions is needed to be able to understand the risk of outcome reporting bias in a review. Consistent guidance in names and definitions for different types of outcomes used in systematic reviews is needed.

Key Words: systematic review, outcome measurement, study inclusion

Word Count: 3616

What is new?

Key findings

- 77% (N=52) of a sample of recent Cochrane Systematic Reviews did not state if and how they used the reporting of outcomes for inclusion of studies
- More than half of the sample used more than 7 primary outcomes contrary to the guidance

What this adds to what is known

- Outcome reporting bias is known to occur in Cochrane reviews. Not knowing how studies were included increases the risk of outcome reporting bias

What is the implication, what should change now?

- Cochrane reviews should better report reasons for including studies that relate to study outcomes

Introduction

The four PICO elements, patients (P), intervention (I), comparator (C) and outcomes (O), together with the type of study design (S), determine the main structure of a systematic review.[1, 2] For decades, the PICO elements have proven an important instrument to determine which exact question is answered by the review because the four elements are used as criteria to include or exclude studies in a review.[3, 4] Recently, the use of outcomes as inclusion criteria has become

more under scrutiny because of the possibility of outcome reporting bias, which would distort the conclusions of a systematic review.[5]

The term outcome itself is ambiguous and can refer to the outcome of the disease process, the effect of an intervention or the quality of a health service.[6, 7] Because different context can lead to different meanings, here, we refer to an outcome as an effect of intervention in the context of Cochrane reviews and not as the outcome as part of the assessment of quality of care. The outcomes in reviews are used to answer the question if an intervention works.

Outcome reporting bias has been defined as a bias that can arise when a trial is excluded from a systematic review or meta-analysis completely, for example, because the results are only reported as “not significant”.[5] Because the outcomes that are not reported are likely to show non-significant effects, a review that excludes these studies would show a too beneficial result. This type of bias should be prevented by contacting authors of the included study and ask them to provide the missing data. If these can’t be obtained, the impact of the missing data should be assessed in a sensitivity analysis.[8] Another, more preventive, solution to this problem is the standardization of outcomes for specific conditions as advocated by the COMET initiative (Core Outcome Measures in Effectiveness Trials). These outcomes should be used and reported in all trials and systematic reviews.[9] However, repeated surveys of Cochrane Reviews between 2007 and 2013 reported that core outcome sets were not used in the reviews.[10, 11] These surveys also found that more than 30% of the Cochrane reviews did not report all pre-specified outcomes, which increases the risk of outcome reporting bias.

Bias can also arise from the way a systematic review uses primary and secondary outcomes for the inclusion of studies. Figure 1 shows the three possible strategies that may underlie inclusion of studies in reviews. When not explicitly reported in the review methods, it is difficult to judge the risk of outcome reporting bias. In general, not using the primary or secondary outcomes as an inclusion criterion (Figure 1, scenario A) is preferred to prevent outcome reporting bias. Sometimes, *only* the primary outcomes are used for inclusion of studies in a systematic review (Figure 1, scenario C). This means that studies that *only* report the secondary outcomes will *not* be included. The included studies that do report the secondary outcome are then only a subset of all available studies that reported these secondary outcomes. As long as the review does not use the secondary outcomes for drawing conclusions on the effectiveness of the intervention, this does not cause new problems. However, the possibility of outcome reporting bias arises when the secondary outcomes are used for the conclusions. Therefore, when authors use primary and secondary outcomes, they should make clear how these have been used for the inclusion of studies and conclusions of the effectiveness of the intervention. In addition, consideration needs to be given to those studies reporting only the secondary outcomes, to assess whether the primary outcome may have been measured but not reported for reasons related to the results, thus inducing outcome reporting bias that would affect the interpretation of the results for the primary outcome.

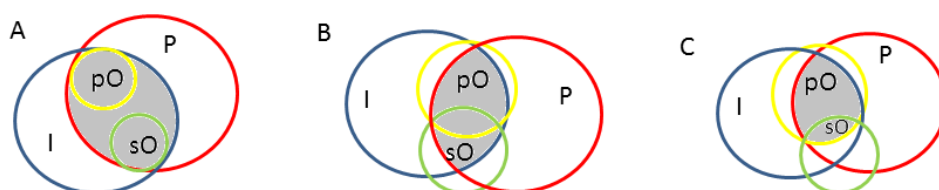


Figure 1: Study inclusion using different criteria for outcomes. A: Inclusion regardless of outcome reported, primary outcomes in yellow circle (pO), secondary outcomes in green circle (sO). B: Inclusion of studies that report either primary outcomes (pO, yellow circle) or secondary outcomes (sO, green circle). C: Inclusion of only studies that report the primary outcome. P (red circle): participants, I (blue circle): Intervention. The grey area represents the included studies

There is detailed information available on how to do a systematic review. The Cochrane Handbook, the PRISMA reporting guideline and the GRADE guidelines are the most authoritative resources.[12-14] However, the information on handling of outcomes, although extensive, still has some gaps and overlaps that lead to varied practice based on interpretation or preference. This holds especially for the number and type of outcomes used as criteria for inclusion of studies in a systematic review and its' effect on conclusions of a review which has not been studied before.

Objective

Our objective is to find out how outcomes in recent Cochrane Reviews were defined and used for inclusion of studies and how current practice compares with existing guidance.

Methods

Assessment of current practice of Cochrane reviews

We located the last review as of August 2016 from each Cochrane Review Group. From the method section and the Summary of Findings (SoF) tables in each review we assessed

- Type of review as being related to treatment directed at curing patients, related to prevention directed at healthy participants, related to both objectives, or related to studying the side-effects (such as pain) of therapeutic or diagnostic procedures;
- Naming of outcomes as provided by the authors;
- Number of primary and secondary outcomes listed in the methods section;
- Type of participants defined either by a specific medical condition (e.g. diabetic) or as healthy persons ;
- If the outcome of review was not related to the medical condition or disease as defined by the type of participants (diabetes status/ HbA1C); In most reviews the participants have a disease and the same disease is the outcome of interest. In that case we noted that there was no difference between the participants and the outcome. Otherwise we noted there was a difference.
- Inferred reason for difference between outcome and participants such as the intervention being preventive or a procedure; The inferred reason for a difference was a preventive intervention when patients were healthy and the outcome was a specific disease outcome for example coronary artery disease. The reason was that the intervention was related to a

procedure when the patients had a disease or various diseases for which a procedure was needed and the outcome was a result of the procedure for example catheter insertion and pain.

- Any statement in methods for use of primary and/or secondary outcomes for inclusion;
- If the authors elaborated how they used outcomes for inclusion and reporting;
- If the authors elaborated inclusion of the outcomes in SoF tables;
- If the authors used search terms for participants, the intervention and/or the outcome;
- How many primary and secondary outcomes were used in the SoF tables;
- Which (primary or secondary or both) outcomes were reported in the abstract as an indication of contributing to the main conclusions of the review.

One reviewer (JV) extracted these data from the reviews into an Excel sheet. The other two authors (SI, CT) checked the data for accuracy. Disagreements were discussed amongst all three until consensus was reached.

Descriptive statistics (frequencies and mean (SD)) were calculated for the extracted data in Excel. We compared how well the sample of reviews complied with guidance on systematic reviews from four documents: . the Cochrane Handbook of reviews of effectiveness of interventions, the Methodological Expectations of Cochrane Intervention Reviews (MECIR) , the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the guidance produced by the working group on Grading of Recommendations Assessment, Development and Evaluation (GRADE).[12-15] We collated the relevant information for the outcome related criteria for inclusion of studies, the naming for different types of outcomes, and the number of outcomes advised. Our findings are detailed below.

The Cochrane Handbook

In paragraph 5.1.2 and 5.4, the Cochrane handbook advises to take the three elements, Participants, Interventions, and Outcomes together with the type of study design as the criteria for inclusion of studies in a review. However, it simultaneously recommends not using the outcomes for searching of studies in the review. The reason for this is to “seek all rigorous studies...irrespective of the outcomes measured or reported” or in other words to avoid outcome reporting bias. This approach works when the review question at hand is defined by the participants and/or the intervention which is the case for most treatments for most patients. For example in a review of specific chemotherapy for breast cancer, the intervention and the participants would be sufficiently specific to include and locate all relevant studies. This approach avoids having to list all possible outcomes that studies could report for breast cancer.

At the same time, the handbook acknowledges in paragraph 5.1.2 that in some cases outcomes have to be used as an inclusion criterion because the participants and the intervention are not specific enough to locate studies. This is the case when the intervention can be studied for other purposes than the disease of interest: when adverse or unusual effects are addressed or when the intervention is preventive. For example, a review on the adverse effects of non-steroidal anti-inflammatory drugs that are used for back pain, omitting the adverse outcomes from search and selection would result in effectiveness related studies: the adverse outcomes would be needed to include the right studies and locate them. However, it has been pointed out that also in these cases there is a serious risk of outcome reporting bias that should be taken into account.[16] If the focus of interest is if a specific medical procedure can reduce pain in a specific patient group, pain as an outcome is needed as an inclusion criterion because the definition of the participants does not include pain. If the focus of the review is on aspirin for preventing cardiovascular outcomes in

healthy persons, cardiovascular outcomes have to be used as a criterion to include and locate relevant studies because aspirin may be used for many conditions. In these cases the participants and the intervention together are still not specific enough to include and locate studies.

The handbook continues with the advice to include *all* outcomes that are meaningful to practitioners and decision makers. It further suggests to use core outcome sets when these are available and to harmonize outcomes across Cochrane reviews for the ease of making ‘overviews’ of multiple systematic reviews.

Finally, the handbook divides the review outcomes in three non-exclusive categories: main, primary and secondary outcomes. Main outcomes are the essential outcomes for decision-making, and those should always be in the ‘Summary of findings’ (SoF) table. These should be restricted to seven outcomes at most and should not ‘generally’ include surrogate or interim outcomes. Primary outcomes are those among the main outcomes that are expected to be analyzed should the review identify relevant studies. Also, the conclusions about the effects of the interventions under review will be largely based on these outcomes. These should be limited to three and include at least one desirable (benefit) and one undesirable (harm) outcome. Secondary outcomes are the remaining main outcomes other than primary outcomes plus any additional outcomes useful for explaining effects. However, the handbook does not give guidance on how to use the primary, secondary or main outcomes for inclusion of studies in an effectiveness review.

MECIR

The MECIR criteria that have been developed based on the handbook and that are used to assure the quality of Cochrane reviews, formulate the guidance on inclusion in different wording but with a similar meaning.[12] MECIR advises that studies should never be excluded from a review solely because no outcomes of interest were reported. This means outcome should not be used as an inclusion criterion alongside participants and intervention. However, they admit that on occasion it will be appropriate to include only studies that measured particular outcomes (for example a multicomponent public health intervention for smoking reduction can exclude studies that don’t report smoking rates). The MECIR conduct standard specifies that authors should clarify in advance whether outcomes listed under ‘Criteria for considering studies for this review’ are used as criteria for including studies (rather than as a list of the outcomes of interest within whichever studies are included).

PRISMA reporting guideline

In the PRISMA reporting guideline, there is no clear definition of main, primary or secondary outcomes.[14] The authors interchangeably used ‘most important’, ‘of primary interest’, or ‘main outcome’ to describe of the same concept. They do use the terms ‘primary’ and ‘secondary’ outcomes in their examples, where adverse effects are listed as secondary outcomes. They ask authors to clearly specify eligibility criteria used in the review: “study eligibility criteria are likely to include the population, the intervention, the comparator, the outcome, and the study designs of interest, as well as other study specific elements, such as specifying a minimum length of follow-up. Authors should state whether studies will be excluded because they do not include (or report) specific outcomes to help readers ascertain whether the systematic review may be biased as a consequence of selective reporting.”

GRADE guidance

The GRADE working group advises to include a maximum of seven outcomes in the SoF table of a systematic review. [17] The group considered this the most amount of information that a reader can grasp. For the development of guidelines, GRADE advises to list up to nine outcomes and divide these into 'critical' and 'non-critical' outcomes.[13] Guideline developers usually consider a number of interventions at the same time and therefore need a number of systematic reviews on the same condition. This makes the approach to the naming and number of outcomes different.

Results

Characteristics of included reviews

We included 52 reviews of which each was the most recently published review from a Cochrane review group (Table 1).

<i>Item surveyed</i>	<i>Categories</i>	<i>Survey findings % (n); mean \pm SD</i>
<i>Type of interventions in Review</i>		
	<i>Treatment</i>	75 % (39)
	<i>Prevention</i>	19 % (10)
	<i>Treatment and prevention</i>	2 % (1)
	<i>Procedures (diagnostic or therapeutic)</i>	4 % (2)
<i>Naming of outcomes</i>		
	<i>Primary and Secondary</i>	90 % (47)
	<i>Main and Secondary</i>	2 % (1)
	<i>Major and Minor</i>	2 % (1)
	<i>Outcomes of interest</i>	2 % (1)
	<i>Primary, secondary and adverse</i>	2 % (1)
	<i>No name</i>	2 % (1)
<i>Number of outcomes in methods section of review</i>		
	<i>Total outcomes per review</i>	8.4 \pm 4.3 Range 2 to 25
	<i>Reviews with more than 7 outcomes</i>	54 % (28)
	<i>Primary outcomes per review</i>	2.5 \pm 1.5
	<i>Reviews with more than 3 primary outcomes</i>	19 % (10)
	<i>Secondary outcomes per review</i>	5.8 \pm 4.1
	<i>Reviews with more than 4 secondary outcomes</i>	56 % (23)
<i>Number of outcomes in Summary of Findings (SoF) tables</i>		
	<i>Total SoF outcomes per review</i>	4.4 \pm 2.2 Range 1 to 8
	<i>Reviews with more than 7 outcomes in SoF</i>	9 % (4)
	<i>Primary outcomes in SoF per review</i>	2.2 \pm 1.5
	<i>Reviews with more than 3 primary outcomes in SoF</i>	28 % (13)
	<i>Secondary outcomes in SoF per review</i>	2.3 \pm 1.9
	<i>Reviews with more than 4 secondary outcomes in SoF</i>	13 % (6)

Table 1. Characteristics of Cochrane reviews (N=52) included in the survey in terms of nomenclature and numbers of their included outcomes; m \pm sd = mean \pm standard deviation

Most reviews evaluated effectiveness of interventions directly aiming to reduce the consequences of the disease while 25% evaluated either preventive interventions such as caries prevention [18] or evaluated the side effects of treatment or medical procedures [19].

The naming of the outcomes used in the reviews was almost always based on the default headings in the RevMan program used for producing Cochrane Reviews: primary and secondary outcomes. Except in two cases where the authors had changed this to major and minor outcomes and to main and secondary outcomes but there was no explanation in the review why this had been changed.[20, 21] In one other review there was no name and again in another review the outcomes were just named “outcomes of interest”.

Most reviews listed more than seven outcomes but kept the number of primary outcomes to three or fewer. The number of outcomes in the Summary of Findings tables was more in line with the guidance with an average of four.

Sometimes, the review authors did not clearly state the relationship between outcome concepts and outcome measures. For example pain is an outcome concept and the various instruments or scales to measure pain are outcome measures. In one review, the authors listed and reported the various pain measures all as different outcomes without an elaboration of the reasons for this, which led to a large number of SoF tables.[22]

Outcomes as criteria to include or exclude studies

The majority of the reviews (77 %) did not specify if or how they used outcomes in their methods section. The methods section of a Cochrane Review contains the heading: ‘Criteria for considering studies for this review’. Under this heading there are Study designs, Participants, Interventions and Outcomes as the criteria. In most cases, there were only criteria under these headings and no elaboration of why these were chosen or how they were used. It is possible that studies were included whenever these reported any of the primary or secondary outcomes but it is also possible that they were only included when they reported one of the primary outcomes (Table 2, Figure 1). A small proportion of the reviews (15 %) explained that they included studies if a study reported any of the primary or the secondary outcomes which is scenario B in figure 1. One review stated that the outcomes were not used for inclusion of studies at all which is scenario A in figure 1.[23] As a consequence they included several studies but could not use the included studies for drawing conclusions because the studies did not report the outcome of interest. Another review detailed the inclusion criteria in an appendix but it was difficult to follow how this had led to inclusion of studies and we categorized this as unclear.[24]

<i>Item surveyed</i>	<i>Categories</i>	<i>Survey findings % (N)</i>
<i>Inclusion criteria explanation</i>		
	<i>Outcome not used for inclusion (A)</i>	2 % (1)
	<i>Inclusion based on either primary or secondary outcome in study (B)</i>	15 % (8)
	<i>Explanation unclear</i>	6 % (3)
	<i>No explanation</i>	77 % (40)
<i>Primary outcome not specified by definition of participants</i>		
	<i>Reviews with different Outcomes and Participants</i>	29 % (15)
<i>Reasons why outcome different from participants</i>		
	<i>Preventive intervention</i>	15 % (8)
	<i>Procedures evaluated</i>	10 % (5)

<i>Only adverse effects evaluated</i>	2 % (1)
<i>Treatment unrelated to disease</i>	2 % (1)
<i>PICO elements used for search</i>	
<i>Search did not include Outcome</i>	70 %
<i>Search did include Outcome</i>	30 %
<i>Secondary outcomes in conclusions</i>	
<i>Not in Summary of Findings</i>	17 % (8)
<i>Not in Abstract</i>	17 % (8)

Table 2. Explanation of inclusion criteria for outcomes in the included Cochrane Systematic Reviews (n=52). A and B refers to the diagrams in figure 1.

Difference between Participants and Outcomes

In a substantial proportion of the reviews (29 %), the definition of the participants was not sufficient to specify the outcome. (Table 2) For example, in a population catheterized long term for urinary tract conditions, the primary outcome was patient satisfaction.[25] Another reason for difference was that the intervention did not directly target the disease of the patients such as interventions to prevent sudden death in patients with epilepsy [26] or where the intervention consisted of a procedure and the outcomes were related to the procedure and not to the disease of interest. The third situation was where participants were healthy persons targeted for primary prevention.

In a third of reviews surveyed (30%), the outcomes were used in the search. Still, 20% of the reviews that contained outcomes that were defined by the disease of the participants used the outcomes in the search. Reviews that included outcomes that were not defined by the disease of the participants used the outcomes in 53% of the cases in their searches.

Use of secondary outcomes in SoF and abstract

In a majority (83%) of the reviews, secondary outcomes, not specified as important for decision making, were reported in the SoF tables or the abstract of the review where the guidance does not recommend this.

Discussion

In the sample of recent Cochrane systematic reviews, 77% of the reviews did not specify if and how the outcomes had been used for inclusion of studies in contrast to guidance. In the other 23% practice ranged from outcomes not being used for inclusion at all, to using both the primary and the secondary outcomes for inclusion or a detailed list of outcomes used for inclusion. Most reviews had more than seven outcomes in the methods section but did comply with guidance to include no more than seven main outcomes in their SoF tables.

Strengths

A strength of our study is that we took a census of all the Cochrane groups' latest reviews accounting for variation across Cochrane Review Groups in terms of types of reviews, types of participants, interventions, outcomes, and methods used. In addition, we systematically extracted data and appraised the elaboration of inclusion criteria in duplicate achieving consensus, increasing the validity of the data. We also looked at aspects of the reviews that are important for the inclusion of studies such as the type of intervention being evaluated being treatment, preventive or procedure associated. With 52 cases included, the confidence interval for 100% of the reviews not giving an

explanation would range from 94% to 100% which is sufficiently narrow to be able to draw conclusions.

Limitations

We included only one review per Cochrane group and therefore we do not claim this to be representative of a group's reviews or policies. We assumed that there will be more variation between groups than within groups because most groups have an established approach of their own in conducting systematic reviews. Taking a sample across groups ensured that this source of variation was taken into account. Some of the issues that we considered, such as the type of review, being preventive or treatment, were based on our interpretation of the data. However, all three authors are experienced systematic reviewers and all data were checked in duplicate and agreed upon which should limit interpretation biases.

Interpretation of the findings

Although the headings in Cochrane reviews clearly state that the four elements Study design, Participants, Interventions and Outcomes have been used for inclusion, our survey shows that it is unclear if this is the case. The MECIR criteria prescribe that there should be an explanation of the inclusion of studies but in most reviews an explanation is missing. This means that the readers of Cochrane reviews cannot always know how the process of including studies has gone based on the information reported in the methods section of the review.

Unclear use of main, and primary and secondary outcomes for inclusion can possibly lead to outcome reporting bias. We don't know of any studies that have compared the effects on secondary outcomes between reviews that included studies based on reporting of primary outcomes only and those that included studies based on reporting either primary or secondary outcomes. After all, if the secondary outcomes are considered minor and less important outcomes that don't play a major role in the analysis, we could imagine that the subset of studies that have reported both the primary and the secondary outcomes are of better quality than those that only report the secondary outcomes. Therefore, it might not be problematic in terms of outcome reporting bias to use only those studies that report the primary outcome as long as the authors take into account the risk of outcome reporting bias for both the primary and the secondary outcomes.

Inclusion of studies that don't measure and report the outcome of interest at all to prevent outcome reporting bias makes it difficult to draw conclusions about outcome reporting bias or otherwise. To readers of the reviews that included studies regardless of outcome reporting, it can be very confusing that studies were included but still no conclusions could be drawn. The ORBIT approach to reduce the risk of outcome reporting bias only allows the exclusion of such studies if there is a statement in the article that the outcome was not measured.[5] However, other guidance documents like MECIR and the Cochrane Handbook leave room for excluding studies based on outcomes in specific situations.[12, 15]

Inclusion of studies that report any of the primary or secondary outcomes makes interpretation of findings also more difficult. There are numerous reviews that include a great number of studies that report the secondary outcome only. To readers of these reviews, it can be a disappointing experience to be offered the effects on a different outcome that was not of main interest. For example, a review on double gloving to reduce wound infection in surgical patients found two studies that reported on the primary outcome, wound infection, but 31 studies that reported on glove perforations, considered a secondary outcome.[27] The conclusions about the effects on the primary outcome were inconclusive but double gloving clearly prevented perforations in the inner

gloves. However, the relation between glove perforations and wound infections is unknown and therefore these results could not be used for drawing conclusions. In our view, it is clearer if the secondary outcomes are only used to support the findings of the primary outcomes. If both wound infection and holes in gloves decreased, this would make a stronger case for the effectiveness of the intervention.

If reviewers want to use primary and secondary outcomes in a review using the primary outcomes for inclusion of studies and using the available secondary outcomes for explanation, they should then acknowledge that, for the secondary outcomes, the studies form only a subset of all studies that have measured the secondary outcomes. (Scenario C in Figure 1) To avoid confusion with the use of primary and secondary outcomes in trials, a name change could be considered. We propose main outcomes for those outcomes that will lead to conclusions about the effectiveness of the intervention as per current Cochrane handbook guidance and explanatory outcomes for those that can support this but would not be sufficient evidence on their own. A logic model can help to explain how the intervention will lead to the outcome, which outcomes are important and which would be explanatory.[28] It would also be helpful to use the ORBIT approach and report a table that shows which studies used which outcome/measurements.[8] (see <http://ctrc.liv.ac.uk/orbit/> for a table generator)

The number of outcomes should be determined by what is useful and interpretable. Given that the average number of outcomes in reviews was more than eight, which has been reported before [10], it is apparently difficult to restrict the number of outcomes. In line with the authors of the GRADE working group, we consider that restricting the number of outcomes would make reviews easier to read and better to understand. One potential way to do so would be to follow guidance by the 'Outcome Measures in Rheumatology' group (OMERACT) which makes a distinction between outcome areas, outcome domains (equivalent to COMET's 'core outcome set'), and outcome measurements.[29] OMERACT distinguishes the following core areas of outcomes: death, life impact, resource use, and pathophysiological manifestations. The group advises that every trial at least includes one outcome domain under each of these core area headings but resource use is not mandatory. For each outcome domain there should be at least one valid outcome measurement defined. This would restrict the number of outcomes to three. It could then be acknowledged that the intervention could also be evaluated with other outcomes and that this could be the topic of another review. This is no different than restricting the number of interventions or the types of participants in a systematic review. Ultimately, a decision-maker wants to know what the most effective intervention is for a specific outcome of their interest. This will always require one or more overviews of reviews or network meta-analyses to determine this.

Comparison with other studies

Other studies that surveyed systematic reviews also concluded that there are issues with the outcomes. Smith et al and Aromataris et al concluded that authors of systematic reviews use too many outcomes.[10, 30] Saldanha et al found that there is no consistent use of outcomes across reviews of various interventions for the same disease.[31] Chow et al studied preferences of patients for the use of cardiovascular disease outcomes in trials.[32] They found that patients had a preference for single outcomes such as stroke or coronary heart disease as opposed to more difficult to interpret composite outcomes such as cardiovascular disease. This indicates that there is a preference for more clarity as opposed to being exhaustive. This supports our conclusion that systematic reviews should include fewer outcomes.

Recently, Clarke et al recommended the use of core outcome sets in systematic reviews.[33] Even though in general core outcome sets are considered important by Cochrane review group coordinating editors [34], we did not see core outcome sets used in the reviews included in this survey. We checked if the topics of the included reviews were covered in the COMET database (<http://www.comet-initiative.org>). Of the topics of the included reviews, 67% was covered in the database but many records only indicated that research was ongoing (no core outcome sets agreed yet). Still, according to our assessment, for 38% of the reviews a published core outcome set could have been included. Two previous surveys of outcome reporting in Cochrane reviews also did not find a description of core outcome sets in any of the reviews published in 2007, 2011, and 2013.[10, 11] It could be that in some cases these were used but that the authors did not describe them as such. We also discussed with some co-ordinating editors within Cochrane. It may be that there is a long history of using relevant outcomes within a review group already before COS were developed and that review groups feel no need to check this within the COS database. It is certainly an issue that warrants further exploration. To enable more prevalent use of core outcome sets in reviews, Cochrane review groups could list the available core outcomes sets applicable to their fields in author resources sections or request that reviews state clearly if they have used these sets.

Implications for practice

Authors of systematic reviews should explain in more detail if and how they used outcomes for inclusion of studies because this is not self-evident. The number of outcomes in a review should be reduced as this will improve the readability and the understanding of the findings of a review.

Review authors should make a distinction between outcome as a concept (the 'what') and as its measurements (the 'how'). In cases where studies are not sufficiently defined by the participants and intervention, the inclusion of studies should also be based on outcome concepts but not on outcome measures.

Implications for research

There is a need for consensus development work on the names and definition of outcome types and their use in Cochrane systematic reviews, including across guidance sources. Clearer distinction between primary and secondary outcomes is also needed for review authors.

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Conflict of Interest:

All three authors are experienced Cochrane reviewers and JV and SI authors on one of the reviews included in this study. JV is also coordinating editor of the Cochrane Work Group. The views presented here are of the authors alone and do not represent either those of Cochrane, Cochrane Work review group, or their respective work organizations.

References

- [1] Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. *Jama*. 1993;270:2093-5.
- [2] Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Annals of internal medicine*. 1997;127:380-7.
- [3] Light RJ, Pillemer DB. Summing up, the science of reviewing research. Cambridge, MA, US: Harvard University Press; 1984.
- [4] Oxman AD, Guyatt GH. Guidelines for reading literature reviews. *Canadian Medical Association Journal*. 1988;138:697-703.
- [5] Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *British Medical Journal*. 2010;340:c365.
- [6] Macbeth HM. Health outcomes, biological, social and economic perspectives. Oxford, UK: Oxford University Press; 1996.
- [7] Donabedian A. Evaluating the quality of medical care. *The Milbank quarterly*. 2005;83:691-729.
- [8] Dwan K, Gamble C, Kolamunnage-Dona R, Mohammed S, Powell C, Williamson PR. Assessing the potential for outcome reporting bias in a review: a tutorial. *Trials*. 2010;11:52.
- [9] Williamson P, Clarke M. The COMET (Core Outcome Measures in Effectiveness Trials) Initiative: Its Role in Improving Cochrane Reviews. *The Cochrane database of systematic reviews*. 2012:ED000041.
- [10] Smith V, Clarke M, Williamson P, Gargon E. Survey of new 2007 and 2011 Cochrane reviews found 37% of prespecified outcomes not reported. *Journal of clinical epidemiology*. 2015;68:237-45.
- [11] Wuytack F, Smith V, Clarke M, Williamson P, Gargon E. Towards core outcome set (COS) development: a follow-up descriptive survey of outcomes in Cochrane reviews. *Syst Rev*. 2015;4:73.
- [12] Higgins J, Lasserson T, Chandler J, Tovey D, Churchill R. *Methodological Expectations of Cochrane Intervention Reviews (MECIR)*. London, UK: Cochrane; 2016.
- [13] Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of clinical epidemiology*. 2011;64:395-400.
- [14] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS medicine*. 2009;6:e1000100.
- [15] Higgins J, Green S. *The Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 ed: Cochrane; 2011.
- [16] Saini P, Loke YK, Gamble C, Altman DG, Williamson PR, Kirkham JJ. Selective reporting bias of harm outcomes within studies: findings from a cohort of systematic reviews. *British Medical Journal*. 2014;349:g6501.
- [17] Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of clinical epidemiology*. 2013;66:158-72.
- [18] Marinho VC. Cochrane reviews of randomized trials of fluoride therapies for preventing dental caries. *Eur Arch Paediatr Dent*. 2009;10:183-91.
- [19] Gajjar K, Martin-Hirsch PP, Bryant A, Owens GL. Pain relief for women with cervical intraepithelial neoplasia undergoing colposcopy treatment. *The Cochrane database of systematic reviews*. 2016;7:CD006120.
- [20] Smith TO, Jepson P, Beswick A, Sands G, Drummond A, Davis ET, et al. Assistive devices, hip precautions, environmental modifications and training to prevent dislocation and improve function after hip arthroplasty. *The Cochrane database of systematic reviews*. 2016;7:CD010815.

- [21] Ewald H, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV infection. The Cochrane database of systematic reviews. 2015:CD006150.
- [22] Stevens B, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. The Cochrane database of systematic reviews. 2000:CD001069.
- [23] Lim CE, Ng RW, Cheng NC, Cigolini M, Kwok C, Brennan F. Advance care planning for haemodialysis patients. The Cochrane database of systematic reviews. 2016;7:CD010737.
- [24] Poorolajal J, Hooshmand E. Booster dose vaccination for preventing hepatitis B. The Cochrane database of systematic reviews. 2016:CD008256.
- [25] Cooper FP, Alexander CE, Sinha S, Omar MI. Policies for replacing long-term indwelling urinary catheters in adults. The Cochrane database of systematic reviews. 2016;7:CD011115.
- [26] Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). The Cochrane database of systematic reviews. 2016;7:CD011792.
- [27] Tanner J, Parkinson H. Double gloving to reduce surgical cross-infection. The Cochrane database of systematic reviews. 2006:CD003087.
- [28] Rohwer A, Pfadenhauer L, Burns J, Brereton L, Gerhardus A, Booth A, et al. Logic models help make sense of complexity in systematic reviews and health technology assessments. *Journal of clinical epidemiology*. 2016.
- [29] Boers M, Kirwan JR, Tugwell P, Beaton D, Bingham III BO, Conaghan PG, et al. The OMERACT handbook: OMERACT; 2016.
- [30] Aromataris E. Ins and outcomes. *JBIM Database System Rev Implement Rep*. 2015;13:1-2.
- [31] Saldanha IJ, Li T, Yang C, Ugarte-Gil C, Rutherford GW, Dickersin K. Social network analysis identified central outcomes for core outcome sets using systematic reviews of HIV/AIDS. *Journal of clinical epidemiology*. 2016;70:164-75.
- [32] Chow RD, Wankhedkar KP, Mete M. Patients' preferences for selection of endpoints in cardiovascular clinical trials. *J Community Hosp Intern Med Perspect*. 2014;4.
- [33] Clarke M, Williamson PR. Core outcome sets and systematic reviews. *Syst Rev*. 2016;5:11.
- [34] Kirkham JJ, Gargon E, Clarke M, Williamson PR. Can a core outcome set improve the quality of systematic reviews?--a survey of the Co-ordinating Editors of Cochrane Review Groups. *Trials*. 2013;14:21.